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# ACYLATIVE DESYMMETRIZATION OF GLYCEROL DERIVATIVES BY CHIRAL DMAP DERIVATIVES

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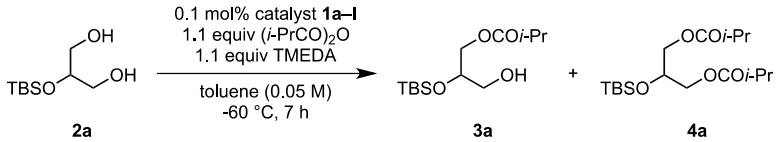
**Abstract** – An efficient enantioselective acylative desymmetrization of glycerol was developed by using a chiral DMAP derivatives **1e** having a 1,1′-binaphthyl unit. The reactions required only 0.1 mol% of the catalyst and showed moderate to good enantioselectivity (up to 94:6 er). Control experiments revealed that the first acylation of a glycerol derivative proceeded selectively rather than the second acylation to give diacylate.

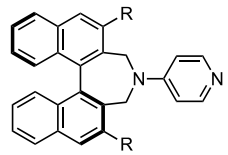
Glycerol is abundantly obtained as a byproduct in the manufacture of biodiesel fuel and used to produce valuable chemicals.[1] It has a distinctive structure that consists of three continuous hydroxy groups within a three-carbon unit. Enantiomerically enriched glycerol derivatives have also been found in biologically active natural products.[2] To obtain such molecules in an enantioselective fashion, enantioselective acylative desymmetrization of glycerol derivatives is one option. For example, several methods have been reported using enzymes,[3] metal catalysts,[4] and organocatalysts.[5] However, the yield and enantioselectivity of a monoacylate still need to be addressed, and the suppression of undesirable over-acylation (diacylation) remains a challenging problem due to the high reactivity of the primary hydroxy group of the resulting monoacylate of glycerol derivatives.

We have been interested in the chemistry of nucleophilic catalysis[6-10] for the acyl transfer reaction[11] and developed a series of chiral *N*,*N*-dimethyl-4-aminopyridine (DMAP) derivatives having a 1,1′-binaphthyl unit possessing polar functional groups (*tert*-alcohol or amide) at the 3,3′-positions. These catalysts have been widely applied to various enantioselective transformations including *O*- to *C*-acyl rearrangements,[7] kinetic resolutions,[8] dynamic kinetic resolution,[10] and desymmetrization of *meso*- or prochiral molecules.[9]

According to our mechanistic studies, hydrogen-bonding interaction between the catalyst and substrate plays an important role in achieving higher levels of enantioselectivity and chemoselectivity. To extend the application of these catalysts to another important class of transformations, we next focused on acylative desymmetrization of glycerol derivatives, which was thought to be a more challenging transformation because of the characteristic structure of glycerol; i.e., three consecutive hydroxy groups including two reactive primary hydroxy groups, and poor lipophilicity in common organic solvents. Both of these characteristics might pose a problem for achieving high enantioselectivity and enhance an undesired over-acylation, which might affect the enantioselectivity of the monoacylate.

**Table 1.** Catalyst screening for the desymmetrization of **2a**[a]



**1a:** R = $C(OH)Ph_2$
**1b:** R = $C(OH)(4\text{-}t\text{-}Bu\text{-}C_6H_4)_2$
**1c:** R = $C(OH)(4\text{-}MeO\text{-}C_6H_4)_2$
**1d:** R = $C(OH)(4\text{-}TBSO\text{-}C_6H_4)_2$
**1e:** R = $C(OH)(4\text{-}TBDPSO\text{-}C_6H_4)_2$
**1f :** R = $C(OH)(4\text{-}TIPSO\text{-}C_6H_4)_2$
**1g:** R = $C(OH)(4\text{-}TIPS\text{-}C_6H_4)_2$
**1h:** R = $C(OH)(3,5\text{-}(t\text{-}Bu)_2\text{-}C_6H_3)_2$
**1i:** R = $C(OH)(3,5\text{-}(MeO)_2\text{-}C_6H_3)_2$
**1j:** R = R = $C(OH)(3,5\text{-}(TIPSO)_2\text{-}C_6H_3)_2$
**1k:** R = $CO_2Et$
**1l:** R = $CONH(4\text{-}MeOC_6H_4)$

| Entry | Catalyst | **3a** (%)[b] | **4a** (%)[b] | Recovery of **2a** (%)[b] | Er of **3a**[c] |
|---|---|---|---|---|---|
| 1 | **1a** | 79 | 9 | 14 | 88:12 |
| 2 | **1b** | 48 | 15 | 36 | 71:29 |
| 3 | **1c** | 60 | 9 | 29 | 79:21 |
| 4 | **1d** | 70 | 10 | 16 | 87:13 |
| 5 | **1e** | 81 | 6 | 10 | 92:8 |
| 6 | **1f** | 72 | 9 | 19 | 89:11 |
| 7 | **1g** | 57 | 10 | 29 | 83:17 |
| 8 | **1h** | 18 | 22 | 61 | 61:39 |
| 9 | **1i** | 50 | 15 | 33 | 84:16 |
| 10 | **1j** | 18 | 38 | 42 | 55:45 |
| 11 | **1k** | 8 | 3 | 87 | 56:44 |
| 12 | **1l** | 19 | 5 | 75 | 49:51 |

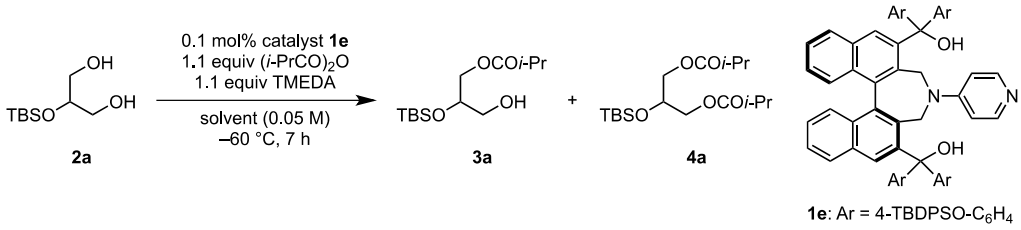
[a]Reactions were performed on a 0.1 mmol scale in toluene (0.05 M) under an argon atmosphere. [b]Yields were determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by HPLC analysis using CHIRALPAK IBN-3.

In this communication, we report the details of the acylative desymmetrization of glycerol derivatives by a chiral DMAP derivative, along with several control experiments to understand these processes.

Initially, the enantioselective acylative desymmetrization of 2-((*tert*-butyldimethylsilyl)oxy)propane-1,3-diol (**2a**)[12] as a model substrate was carried out with selected catalysts **1a**–**l** (0.1 mol%) in the presence of 1.1 equiv of isobutyric anhydride[13] and 1.1 equiv of *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) in toluene (0.05 M) at –60 ºC for 7 h. (Table 1). The use of catalyst **1a** with *tert*-alcohol units having a diphenyl group gave monoacylate **3a** in good yield with a good enantiomeric ratio (er) (entry 1, 79% yield of **3a**; 88:12 er) along with undesired diacylate **4a** (9% yield). The catalyst **1b**–**g** with *tert*-alcohol units having a 4-substituted aryl group also afforded **3** in 48–81% yield with good enantioselectivity along with detectable amount of diacylate **4a** (entries 2–7, up to 92:8 er for **3a**). On the other hand, catalyst **1h**–**j** having 3,5-disubstituted aryl groups resulted in poor to moderate yield of **3a** (up to 84:16 er) and a significant amount of diacylate was detected (entries 8–10). Furthermore, ester or amide groups on the catalyst showed poor catalytic activity and almost no enantioselectivity (entries 11 and 12, up to 56:44 er). According to these results, catalyst **1e** was selected as an optimal catalyst for further screening of the reaction conditions.

Next, we screened various solvents for the desymmetrization of **2a** with **1e** at –60 ºC for 7 h (Table 2). The reactions in ethereal solvents showed moderate yields but good enantioselectivity of monoacylates (entries 2–5, up to 92:8 er). The reactions in other common organic solvents ($CH_2Cl_2$, EtOAc, acetone) resulted in somewhat lower enantioselectivity (entries 6–8, up to 89:11 er). After considering these results, we selected toluene as the solvent for further optimization of the reaction conditions.

**Table 2.** Effects of solvent for the desymmetrization of **2a**[a]

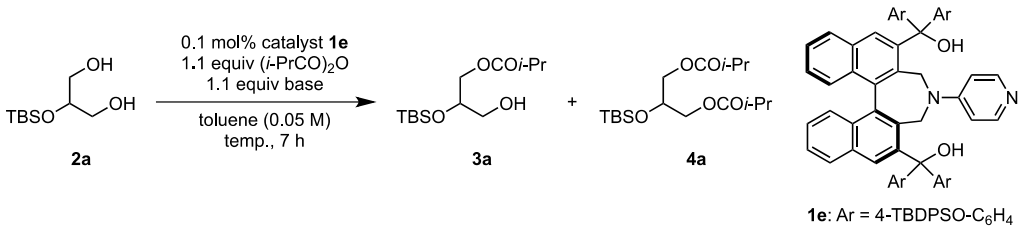



| Entry | Solvent | **3a** (%)[b] | **4a** (%)[b] | Recovery of **2a** (%)[b] | Er of **3a**[c] |
|---|---|---|---|---|---|
| 1 | toluene | 81 | 6 | 10 | 92:8 |
| 2 | *t*-BuOMe | 43 | <2 | 58 | 71:29 |
| 3 | CPME[d] | 72 | 2 | 27 | 92:8 |
| 4 | $Et_2O$ | 59 | 2 | 43 | 90:10 |
| 5 | THF | 43 | 3 | 53 | 91:9 |
| 6 | $CH_2Cl_2$ | 68 | 5 | 29 | 87:13 |
| 7 | EtOAc | 47 | 3 | 49 | 89:11 |
| 8 | acetone | 60 | 3 | 41 | 89:11 |

[a]Reactions were performed on a 0.1 mmol scale in solvent (0.05 M) under an argon atmosphere. [b]Yields were determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by HPLC analysis using CHIRALPAK IBN-3. [d]Cyclopentyl methyl ether.

We then tested selected bases and the reaction temperature for the desymmetrization of **2a** with **1e** for 7 h (Table 3). The reactions in the presence of triethylamine showed the highest yield of **3a** with high enantioselectivity compared to TMEDA (91% yield of **3a**; 92.5:7.5 er; entry 2 vs 1). The use of *N*,*N*-diisopropylethylamine resulted in a lower yield of **3a** and a significant amount of unreacted **2a** was recovered (70% yield of **3a**; 93:7 er; entry 3). The effects of the reaction temperature in the presence of triethylamine were also examined (entries 4–6 vs 2). The reaction at –20 or –40 °C proceeded smoothly, but the enantioselectivity was only moderate (85:15 er and 89:11 er, respectively, entries 4 and 5). On the other hand, the reaction at –78 °C proceeded incompletely, but the enantioselectivity was slightly improved (78% yield of **3a**; 93:7 er; 18% recovery of **2a**; entry 6). Based on these results, the reaction at –60 °C was satisfactory with respect to both the yield of **3a** and enantioselectivity. Accordingly, the optimal reaction conditions were set as follows: 0.1 mol% of catalyst **1e**, 1.1 equiv of isobutyric anhydride, and 1.1 equiv of triethylamine in toluene (0.05 M) at –60 °C for 7 h.

**Table 3.** Effects of base and reaction temperature for the desymmetrization of **2a**[a]




| Entry | Base | Temp. (°C) | **3a** (%)[b] | **4a** (%)[b] | Recovery of **2a** (%)[b] | er of **3a**[c] |
|---|---|---|---|---|---|---|
| 1 | TMEDA | –60 | 81 | 6 | 10 | 92:8 |
| 2 | $Et_3N$ | –60 | 91 | 6 | 2 | 92.5:7.5 |
| 3 | *i*-$Pr_2NEt$ | –60 | 70 | 4 | 26 | 93:7 |
| 4 | $Et_3N$ | –20 | 93 | 8 | <2 | 85:15 |
| 5 | $Et_3N$ | –40 | 92 | 5 | <2 | 89:11 |
| 6 | $Et_3N$ | –78 | 78 | 4 | 18 | 93:7 |

[a]Reactions were performed on a 0.1 mmol scale in solvent (0.05 M) under an argon atmosphere. [b]Yields were determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by HPLC analysis using CHIRALPAK IBN-3.

The desymmetrization of an array of glycerol derivatives with different protecting groups was examined under the optimal conditions (Figure 1).

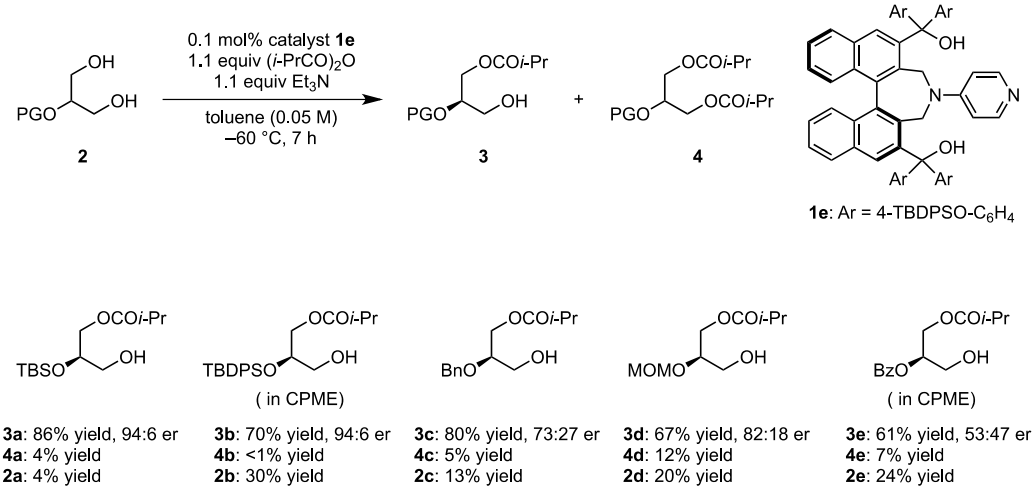
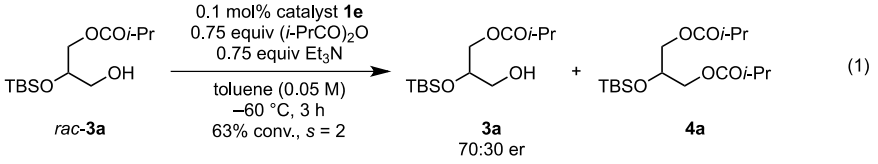


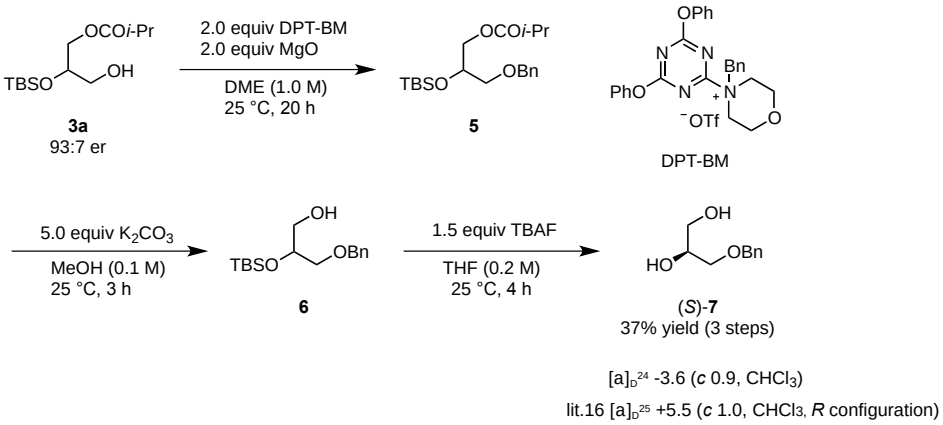

**Figure 1.** Desymmetrization of various glycerol derivatives by catalyst **1e**

The reaction of **2a** (PG = TBS) afforded monoacylate **3a** in good yield with high enantioselectivity (86% isolated yield with 94:6 er) along with 4% of diacylate **4a** and 4% recovery of **2a**. In addition, the use of a bulkier silyl protecting group **2b** (PG = TBDPS) showed acceptable results (70% yield of **3b** with 94:6 er and 30% recovery of **2b**), but in this case a more polar solvent, CPME, was required to dissolve diol **3b**. Other protecting groups, such as **2c** (PG = Bn), **2d** (PG = MOM) and **2e** (PG = Bz), resulted in moderate to good yields of monoacylate **3c**–**e** with lower enantioselectivities, and detectable amounts of diacylates and unreacted diols were observed. One possible reason for such poor results might involve barely soluble diols **2c**–**e** which lead to incomplete enantiodiscrimination by catalyst **1e**. The solubility of monoacylate **3c**–**e** was much higher than that of diols **2c**–**e**. Accordingly, once **3c**–**e** was generated, it was readily converted to diacylate **4c**–**e**. For the successful enantioselective desymmetrization of glycerol derivatives, a silyl protecting group (e.g., diol **3a**) is indispensable for improving the solubility of glycerol derivatives.

Undesirable over-acylation to form diacylates undoubtedly affects the yields and/or enantioselectivity of monoacylates. To clarify the enantioselectivity of the second acylation process, a racemate of monoacylate **3a** was subjected to similar reaction conditions (0.75 equiv of $(i\text{-PrCO})_2O$ and $Et_3N$) (eq. 1). Over-acylation was relatively fast and gave the corresponding diacylate **4a** in 63% conversion in 3 h, but the selectivity factors[14] were low ($s$ =2). Analysis of the recovered starting material **3a** revealed that monoacylate **3a** (minor enantiomer of the first acylation) was preferentially consumed. This result suggested that the over-acylation process involved kinetic resolution and tended to increase the enantio-enrichment of **3a**, but its selectivity was rather low.



Finally, the absolute configuration of monoacylate **3a** was determined by comparison to a known compound (Scheme 1). Benzylation of monoacylate **3a** (93:7 er) using DPT-BM[15] under mild conditions gave product **5**, and the subsequent removal of an acyl group and silyl group of **5** gave diol **7**, the absolute configuration of which was determined to be *S* by comparison to the specific optical rotation reported for (*R*)-**7**.[16] Based on this result, monoacylate **3a** have an *R* configuration, and monoacylates **3b**–**e** were also assigned *R* by analogy.




**Scheme 1.** Determination of the absolute configuration of **3a**

In summary, we have demonstrated that a small amount of catalyst **1e** efficiently promoted an enantioselective acylative desymmetrization of glycerol derivatives. The reactions required only 0.1 mol% of the catalyst and showed moderate to good enantioselectivity (up to 94:6 er). Control experiments revealed that the first acylation proceeded enantio- and chemoselectively rather than the second acylation to give diacylate. Further applications of these products to the synthesis of biologically important molecules are now in progress.

## ACKNOWLEDGEMENTS

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## SUPPORTING INFORMATION

Supplementary data (analytical data for reaction products) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27191/102/6.

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12. Initial screening of the substrate structure revealed that protection of the 2-hydroxy group was important for improvement of substrate solubility in common organic solvents, and for achieving high enantioselectivity and chemoselectivity.
13. Based on our previous report, isobutyric anhydride as an acylation reagent showed the higest enantioselectivity of monoacylate compared to isobutyric chloride or acetic anhydride. See, ref 8.
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17. **General Procedure for the desymmetrization of 2-*O*-protected glycerol derivatives with catalyst 1e under optimal conditions**

    When 0.1 mol% of the catalyst was used in the reaction, a solution of the catalyst in $CHCl_3$ (10.0 mM) was prepared in advance. This stock solution was added to a test tube, and then the solvent was removed. The resulting catalyst was used for the following reaction.

    To a solution of catalyst **1e** (0.1mol%), substrate **2a**–**e** (1.0 equiv), and $Et_3N$ (1.1 equiv) in dry toluene or CPME (0.05 M) was added $(i\text{-PrCO})_2O$ (1.1 equiv) at –60 °C. MeOH (2 mL) was added to quench the reaction and the mixture was stirred for 30 min at room temperature. $H_2O$ (10 mL) was added, and the mixture was then extracted with EtOAc (10 mL×3), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude mixture. Purification of the crude product by flash column chromatography on silica gel (eluent: hexane/EtOAc = 3:1 to 1:3, v/v) gave the monoacylate **3a**–**e**, diacylate **4a**–**e** and recovery of substrate **2a**–**e**. The enantiomeric ratios were determined by HPLC analysis.